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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,795	02/22/2002	Fredrik Kamme	PRI-0021 (ORT-1508)	9944

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EXAMINER

KIM, YOUNG J

ART UNIT PAPER NUMBER

1637

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/080,795

Applicant(s)

KAMME ET AL.

Examiner

Young J. Kim

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-14 and 16-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-14 and 16-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date. _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' Brief in response to Examiner's Final Rejection mailed on July 27, 2006 is acknowledged.

Applicants are advised that the Brief was defective for not complying with the provisions set forth in 37 CFR 44.37(c)(1)(v), which requires a Brief to state a concise explanation of the subject matter defined in each of the independent claims involved in the appeal.

Applicants do not separately disclose the required concise explanation of independent claims 1 and 14, but rather, provides a single explanation. While the Brief is defective, as the present examiner came across a prior art teaching(s) which would better make a *prima facie* showing for an appeal process, the finality of the previous Office Action is hereby withdrawn and the instant Office Action is provided herein. Applicants are advised to consider this guidance when filing a subsequent Brief, so as to preclude the possibility of holding their Brief, defective.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-14, 16, and 18-23 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method wherein Bst DNA polymerase is not involved in a reaction temperature of 80°C, does not reasonably provide enablement for said method, wherein Bst DNA polymerase is involved in a reaction temperature of 80°C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/use the invention commensurate in scope with these claims.

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Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in *In Re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

Nature of the Invention and Enablement Issues:

The nature of the invention relates to a method of generating an amplified cRNA molecules, wherein the method involves the generation of a first strand cDNA molecule from a total or mRNA molecules of a sample, followed by the generation of a second strand cDNA molecule from said first strand cDNA molecule, said generation of said second strand cDNA molecule being effected by Bst DNA polymerase, large fragment.

The enablement issue surrounds the entire scope of the instantly rejected claims, which embraces a reaction temperature involving Bst DNA polymerase, large fragment, the temperature of which, is known and accept in the art as inactivating said Bst DNA polymerase.

State of prior art:

Bacallao et al. (U.S. Patent No. 7,186,507 B2, issued March 6, 2007), explicitly states that Bst DNA polymerase, large fragment is, “[h]eat inactivated by incubation at 80°C for 10 minutes.” (column 13, lines 1-5).

The instant application contemplates an incubation time from one to sixty minutes for the generation of a second strand cDNA molecule with a Bst DNA polymerase, large fragment (see claim 4, for example).

Conclusion:

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As the prior art is clear, the reaction temperature claimed by the instant claims embrace a temperature range which is explicitly disclosed by prior art, as inactivating Bst DNA polymerase, large fragment. An inactivated Bst DNA polymerase cannot generate a second strand cDNA molecule.

Applicants are invited to submit a showing that the invention as claimed at the non-enabled temperature, is in fact, enabled should Applicants desire to overcome the instant rejection.

For the above reasons, it is determined that a skilled artisan would not be able to conduct a method fully commensurate in scope of the claims without undue experimentation.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 2, 4-14, and 16-23 under 35 U.S.C. 103(a) as being unpatentable over Mack et al. (U.S. Patent No. 6,566,502 B1, issued May 20, 2003, filed June 30, 2000) in view of Legerski (U.S. Patent No. 6,406,891 B1, issued June 18, 2002, filed September 28, 1998), made in the Office Action mailed on December 27, 2005 is withdrawn based on a careful reconsideration.

New Grounds

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The rejection of claims 1, 2, 4-14, and 16-23 under 35 U.S.C. 103(a) as being unpatentable over Mack et al. (U.S. Patent No. 6,566,502 B1, issued May 20, 2003, filed June 30, 2000) in view of Bacallao et al. (U.S. Patent No. 7,186,507 B2, issued March 6, 2007, priority December 9, 1999¹).

Mack et al. disclose a method of producing cRNA from samples, said method comprising the steps of:

- (a) synthesizing a first strand cDNA from total RNA or polyA+ mRNA by contacting said RNA or polyA+ mRNA with T7-T24 oligo (or a first primer) and SuperScript™ RT (or reverse transcriptase) (column 44, lines 33-41);
- (b) synthesizing a second strand cDNA via contacting the synthesized first cDNA strand with *E. coli* DNA polymerase and RNase H (column 44, lines 42-54); and
- (c) In vitro Transcription (IVT) of cDNA into cRNA by contacting the synthesized double stranded cDNA with a T7 RNA polymerase (column 45, lines 1-16).

Mack et al., in producing a second cDNA strand, do not explicitly use Bst DNA polymerase, large fragment, and incubation conditions thereof (claims 2, 4, 6, 12, and 17).

Bacallao et al. disclose a method of generating a plurality of cRNAs, wherein the artisans first reverse transcribe a first strand cDNA (column 12, lines 42-43).

Upon generation of the first strand cDNA, the artisans disclose the following:

“Having produced the first strand cDNA species using reverse transcription, the present invention also contemplates the **use of various DNA polymerases to produce the second strand of the double-stranded cDNA moiety. Exemplary polymerases are as described below. Bst DNA Polymerase, Large Fragment...**” (column 12, lines 42-43; Bacallao et al.)

¹ U.S. Patent 7,186,507, is a national phase of PCT/US00/33460, filed after November 29, 2000, designating U.S. as one of the countries, and published in English. Under the amended AIPA act, the 102(e) date for such national phase application, when issued as a patent, is entitled to an effective filing date of the application through the provisional application of, filed on December 9, 1999).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made combine the teachings of Mack et al. with the teachings of Bacallao et al., thereby arriving at the claimed invention for the following reasons.

All of the steps claimed by the instant claim are disclosed by Mack et al., excepting that the polymerase used for second strand cDNA synthesis is an *E. coli* DNA polymerase. Specifically, Mack et al, in generating the 2nd strand of the cDNA, employ *E. coli* DNA polymerase.

Consequently, Mack et al. would not disclose a condition that is suitable for a second strand cDNA synthesis involving Bst DNA polymerase large fragment.

However, Bacallao et al. **explicitly disclose a method of generating a second strand cDNA to form a** double stranded cDNA, wherein the artisans explicitly disclose and contemplate the use of Bst polymerase, large fragment.

In addition, Bacallao et al. explicitly disclose that when employing Bst polymerase, the reaction temperatures above 70°C, “are not recommended.” (column 13, lines 1-4).

Hence, one of ordinary skill in the art would have been motivated to employ the teachings of Bacallao et al., in the method of generating the double stranded cDNA molecules of Mack et al., for the above discussed benefit in generating second strand cDNA molecules from its first strand cDNA.

With regard to claims 2 and 17, given the fact that Bacallao et al. disclose the use of Bst DNA polymerase large fragment for second-strand cDNA synthesis, one of ordinary skill in the art would have been able to determine the optimal temperature at which to conduct this step. In addition, as already discussed, Bacallao et al. explicitly discloses that Bst DNA polymerase should not exceed 70°C (column 13, lines 1-4).

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With regard claims 4, 6 and 12, the incubation time/concentrations of the Bst DNA polymerase large fragment and RNase, given the fact that Bst DNA polymerase is employed, the optimal concentration or incubation temperature under which the method is conducted is obvious under the routine optimization, as provided for by MPEP 2144.05(II).

“A. Optimization Within Prior Art Conditions or Through Routine Experimentation
Generally, *differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.*” [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”); < ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).”

Hence, it would have been well-within the purview of an ordinarily skilled artisan at the time the invention was made to be motivated to determine the optimum incubation condition, *i.e.*, temperature and the incubation time, as well as the enzyme concentration, through routine optimization, provided that Bacallao et al. explicitly disclose the use of Bst DNA polymerase large fragment in generating second strand cDNA molecules in a RT-PCR reaction, thereby arriving at the claimed invention.

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With regard claim 5, Mack et al. employs labeled Bio-11-UTP and Bio-16-CTP (column 45, lines 11-13).

With regard claims 7, 8, 9, 10, and 18, Mack et al. states that the nucleic acids could be labeled with Cy_3 or Cy_5 (column 17, lines 16-20; column 31, lines 40-43).

With regard to claims 11, 22 and 23, the labeled cRNA are hybridized on an array of nucleic acid probes to determine the differential expression of CZA8 (column 48) in tumorous (thus pathologically aberrant) and normal samples (thus pathologically non-aberrant; *see* column 59, claim 1).

With regard to claims 13 and 19-21, while Mack et al. are not explicit in disclosing how many polynucleotides probes are immobilized on their array, Mack et al. disclose that known commercial arrays could be used in their method, including Affymetrix GeneChipTM (column 26, line 26), which is known in the art to comprise over 1,000 probes/cm². According to *In re Best* 195 USPQ 430, 1997, the court stated that, "Patent Office can require applicant to prove that prior art products do not necessarily or inherently possess characteristics of his claimed product wherein claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes; burden of proof is on applicant" (pp. 430). Absent evidence to the contrary, the density of the array claimed by the instant application is determined to be met by Mack et al.

With regard to claim 16, the samples employed are from human patient (thus mammalian; *see* column 4, lines 23-30).

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Applicant's arguments with respect to previous rejection of record have been considered but are moot in view of the new ground(s) of rejection, involving a prior art teaching which clearly

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demonstrates the use of Bst DNA polymerase, large fragment for generating a second strand cDNA, in a RT-PCR reaction.

Conclusion

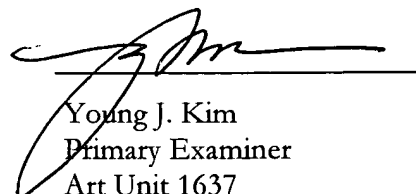
No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.



Young J. Kim
Primary Examiner
Art Unit 1637
4/9/2007

**YOUNG J. KIM
PRIMARY EXAMINER**

YJK